

PCT**NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

30 March 2001 (30.03.01)

International application No.

PCT/US00/19747

Applicant's or agent's file reference

RTSP-0065

International filing date (day/month/year)

20 July 2000 (20.07.00)

Priority date (day/month/year)

23 July 1999 (23.07.99)

Applicant

MONIA, Brett, P. et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

16 February 2001 (16.02.01)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Zakaria EL KHODARY

Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/19747

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/00, 15/11; C12Q 1/68; A61K 48/00

US CL : 435/6, 366, 375, 91.1; 536/23.1, 24.3, 24.5; 514/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 366, 375, 91.1; 536/23.1, 24.3, 24.5; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | BRANCH, A. D. A good antisense molecule is hard to find. TIBS. February 1998, Vol. 23, pages 45-50, see entire document. | 12-18 |
| X, Y | WO 98/54203 A1 (MERCOLA, DANIEL) 03 December 1998 (03/12/98), see entire document, especially column 14, line 26. | 1-2, 5-11, 15 |
| Y | CROOKE, S.T. 'Basic Principles of Antisense Therapeutics.' In: Antisense Research and Application. 1998, pages 3-49, see entire document. | 5-11 |
| Y | UHLMANN et al. Antisense oligonucleotides: A New Therapeutic Principle. Chemical Reviews. June 1990, Vol. 90, No. 4, pages 543-584, see entire document. | 5-11 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|--|---|
| * Special categories of cited documents | * T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| * A* document defining the general state of the art which is not considered to be of particular relevance | * X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| * E* earlier document published on or after the international filing date | * Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| * L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | * G* document member of the same patent family |
| * O* document referring to an oral disclosure, use, exhibition or other means | |
| * P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

15 SEPTEMBER 2000

Date of mailing of the international search report

18 OCT 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MARY SCHMIDT

Telephone No. (703) 308-0196

NOV 07 2000

PCT

From the INTERNATIONAL BUREAU

To:

LICATA, Jane, Massey
Law Offices of Jane Massey Licata
66 E. Main Street
Marlton, NJ 08053
ETATS-UNIS D'AMERIQUE

**NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

| | |
|---|---|
| Date of mailing (day/month/year) 25 October 2000 (25.10.00) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference RTSP-0065 | |
| International application No. PCT/US00/19747 | |
| International filing date (day/month/year) 20 July 2000 (20.07.00) | |
| International publication date (day/month/year) Not yet published | Priority date (day/month/year) 23 July 1999 (23.07.99) |
| Applicant ISIS PHARMACEUTICALS, INC. et al | |

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| <u>Priority date</u> | <u>Priority application No.</u> | <u>Country or regional Office or PCT receiving Office</u> | <u>Date of receipt of priority document</u> |
|-------------------------|---------------------------------|---|---|
| 23 July 1999 (23.07.99) | 09/359,756 | US | 29 Augu 2000 (29.08.00) |

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Marc Salzman

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

NOV 13 2001

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITYTo: LICATA, JANE MASSEY
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NEW JERSEY 08053-1000✓
✓
np = 1-23-02

PCT

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

07 NOV 2001

Applicant's or agent's file reference

RTSP-0065

IMPORTANT NOTIFICATION

International application No.

PCT/US00/19747

International filing date (day/month/year)

20 JULY 2000

Priority Date (day/month/year)

23 JULY 1999

Applicant

ISIS PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MARY SCHMIDT

Dorothy Lawrence For
Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|--|--|--|
| Applicant's or agent's file reference RTSP-0065 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US00/19747 | International filing date (day/month/year) 20 JULY 2000 | Priority date (day/month/year) 23 JULY 1999 |
| International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet. | | |
| Applicant ISIS PHARMACEUTICALS, INC. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 4 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|--|--|
| Date of submission of the demand 16 FEBRUARY 2001 | Date of completion of this report 30 SEPTEMBER 2001 |
| Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 | Authorized officer  MARY SCHMIDT |
| Facsimile No. (703) 305-3230 | Telephone No. (703) 308-0196 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/19747

I. Basis of the report**1. With regard to the elements of the international application: ***☐ the international application as originally filed☒ the description:pages 1-80 , as originally filedpages NONE , filed with the demandpages NONE , filed with the letter of _____☒ the claims:pages 81-82 , as originally filedpages NONE , as amended (together with any statement) under Article 19pages NONE , filed with the demandpages NONE , filed with the letter of _____☒ the drawings:pages NONE , as originally filedpages NONE , filed with the demandpages NONE , filed with the letter of _____☒ the sequence listing part of the description:pages NONE , as originally filedpages NONE , filed with the demandpages NONE , filed with the letter of _____**2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.**

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:**☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.**4. ☒ The amendments have resulted in the cancellation of:**☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig NONE**5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).****

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)

Claims 3-18 YESClaims 1-2 NO

Inventive Step (IS)

Claims 3-4, 16-18 YESClaims 1-2, 5-15 NO

Industrial Applicability (IA)

Claims 1-18 YESClaims NONE NO**2. citations and explanations (Rule 70.7)**

Claims 1-2 lack novelty under PCT Article 33(2) as being anticipated by Mercola et al. The claims are drawn to antisense oligonucleotides to human MEKK1. Mercola et al. teach antisense to human MEKK1 (see page 14, line 26, for instance).

Claims 5-15 lack an inventive step under PCT Article 33(3) as being obvious over Mercola et al. in view of Milner et al, Crooke and Uhlmann et al.

Mercola et al. is relied upon as set forth above to teach antisense to human MEKK1. Milner et al. is relied upon to teach screening a known gene in the art for antisense to said gene. Crooke et al. and Uhlmann et al. are relied upon to teach modifications to antisense oligonucleotides for improved stability of said antisense oligonucleotides.

It would have been obvious to make antisense oligonucleotides to human MEKK1 for expression of said antisense to cells in culture as taught by Mercola et al. It would have been further obvious to screening for other antisense to the MEKK1 gene as taught by Milner et al. since Mercola et al. provide the motivation to make antisense to the human MEKK1 gene. It would have been further obvious to modify antisense oligonucleotides with the modifications taught by Crooke and Uhlmann et al. for improved stability of the antisense oligonucleotides.

Claims 3-4 and 16-18 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the specific antisense oligonucleotides to human MEKK1 of claims 3-4 nor therapeutic expression in cells in whole organisms of antisense to human MEKK1.

----- NEW CITATIONS -----

none

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): C12N 15/00, 15/11; C12Q 1/68; A61K 48/00 and US Cl.: 435/6, 366, 375, 91.1; 536/23.1, 24.3, 24.5; 514/44

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/19747

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/00, 15/11; C12Q 1/68; A61K 48/00

US CL : 435/6, 366, 375, 91.1; 536/23.1, 24.3, 24.5; 514/44

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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|-----------|--|-----------------------|
| A | BRANCH, A. D. A good antisense molecule is hard to find. TIBS. February 1998, Vol. 23, pages 45-50, see entire document. | 12-18 |
| X, Y | WO 98/54203 A1 (MERCOLA, DANIEL) 03 December 1998 (03/12/98), see entire document, especially column 14, line 26. | 1-2, 5-11, 15 |
| Y | CROOKE, S.T. 'Basic Principles of Antisense Therapeutics.' In: Antisense Research and Application. 1998, pages 3-49, see entire document. | 5-11 |
| Y | UHLMANN et al. Antisense oligonucleotides: A New Therapeutic Principle. Chemical Reviews. June 1990, Vol. 90, No. 4, pages 543-584, see entire document. | 5-11 |



Further documents are listed in the continuation of Box C.



See patent family annex.

| | | | |
|--|---|-----|--|
| * Special categories of cited documents: | | * T | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| * A | document defining the general state of the art which is not considered to be of particular relevance | * X | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| * E | earlier document published on or after the international filing date | * Y | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| * L | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | * & | document member of the same patent family |
| * O | document referring to an oral disclosure, use, exhibition or other means | | |
| * P | document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search

15 SEPTEMBER 2000

Date of mailing of the international search report

18 OCT 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MARY SCHMIDT

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/19747

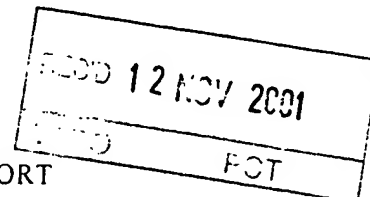
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| Y | MILNER et al. Selecting effective antisense reagents on combinatorial oligonucleotide arrays. Nature biotechnology. June 1997, Vol. 15, pages 537-541, see entire document. | 5-11 |

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)




| | | |
|--|--|--|
| Applicant's or agent's file reference RTSP-0065 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US00/19747 | International filing date (day/month/year) 20 JULY 2000 | Priority date (day/month/year) 23 JULY 1999 |
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| Applicant ISIS PHARMACEUTICALS, INC. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

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3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
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| Date of submission of the demand 16 FEBRUARY 2001 | Date of completion of this report 30 SEPTEMBER 2001 |
| Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 | Authorized officer  MARY SCHMIDT |
| Facsimile No. (703) 305-3230 | Telephone No. (703) 308-0196 |

I. Basis of the report**1. With regard to the elements of the international application: ***

- ☐ the international application as originally filed
- ☒ the description:
pages 1-80 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____
- ☒ the claims:
pages 81-82 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____
- ☒ the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____
- ☒ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

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- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

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- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
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- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

| | | |
|-------------------------------|--------------------------|-----|
| Novelty (N) | Claims <u>3-18</u> | YES |
| | Claims <u>1-2</u> | NO |
| Inventive Step (IS) | Claims <u>3-4, 16-18</u> | YES |
| | Claims <u>1-2, 5-15</u> | NO |
| Industrial Applicability (IA) | Claims <u>1-18</u> | YES |
| | Claims <u>NONE</u> | NO |

2. citations and explanations (Rule 70.7)

Claims 1-2 lack novelty under PCT Article 33(2) as being anticipated by Mercola et al. The claims are drawn to antisense oligonucleotides to human MEKK1. Mercola et al. teach antisense to human MEKK1 (see page 14, line 26, for instance).

Claims 5-15 lack an inventive step under PCT Article 33(3) as being obvious over Mercola et al. in view of Milner et al, Crooke and Uhlmann et al.

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Claims 3-4 and 16-18 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the specific antisense oligonucleotides to human MEKK1 of claims 3-4 nor therapeutic expression in cells in whole organisms of antisense to human MEKK1.

----- NEW CITATIONS -----

none

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): C12N 15/00, 15/11; C12Q 1/68; A61K 48/00 and US Cl.: 435/6, 366, 375, 91.1; 536/23.1, 24.3, 24.5; 514/44